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An in silico study on Antidiabetic activity DPP-IV inhibitors and bioactive compounds *Boesenbergia pandurata* Roxb

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Abstract. Diabetes type 2 is a disease caused by a metabolic disorder. One of treatment of type 2 diabetes mellitus is focused on incretin hormone. Glucagon like peptide – 1 (GLP-1) is a insulintropic agent and plays a role in regulation of blood glucose. GLP-1 interacts with GLP-1R so the blood sugar level increases. DPP – IV is inhibitor are important biological target related for the treatmen of type 2 diabetes mellitus. DPP-IV inhibitor from drug synthetic have some side effect therefore develop natural DPP-IV inhibitor by in silico approaches. This research is study molecular interaction between DPP – IV inhibitor drug synthetic on the market was sitagliptin, vildagliptin, saxagliptin, anagliptin and alogliptin with compare bioactive ligan from *Boesenbergia pandurata* Roxb such as alipinetin, pinocembrin, pinostrobin, cardamonin, panduratin. The metodology used in the research is molecular docking using docking software. The results showed that DPP – IV inhibitor with vildagliptin had the best binding energy 15.49 Kcal/mol and torsional energy 19.69. Based on the analysis of docking in silico DPP-IV inhibitors with active compound *Boesenbergia pandurata* Roxb has binding energy 2.39 Kcal/mol and torsional energy 5.5 and can be used as an antidiabetic drug candidate.

Keywords : In Silico, Dipeptidyl peptidase IV, *Beosenbergia pandurata* Roxb, GLP-1, Diabetes mellitus, molecular docking.

1. Introduction

Diabetes Mellitus is a disease caused by a metabolic disorders with a marked increase blood glucose levels. The global prevalence of diabetes in adults has increased over the past few decades (1). The prevalence of diabetes in the worldwide for all age groups is estimated to be 2.8% in 2000 and 4.4% in 2030. The number of diabetics is predicted to increase from 171 million people in 2000 to 366 million people in 2030. Diabetics on cities in developing countries is predicted to double between 2000 and 2030 (2). Diabetes mellitus classified in two general categories, type 1 diabetes mellitus characterized is due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency. Type 2 diabetes mellitus is due to loss of β-cell insulin secretion frequently on the background of insulin resistance (3).

For the treatment of diabetes based on drugs available on the market such as insulin, secretagogues groups (such as sulfonylureas and incretins), and hypoglycemia groups (such as biguanides, thiazolidinediones) and drug combinations in different groups. These drugs are effective but can cause side effects such as heart complications, bone density loss, weight gain, digestive problems and urinary tract infections, therefore the development and challenges the search for new drugs diabetes mellitus is continuously carried out (4).

Recently the treatment of type 2 diabetes mellitus has focused on incretin hormone. Glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are the main incretin hormones secreted by intestinal cells. GLP-1 plays a role in the regulation of blood glucose levels because of their biological actions, such as stimulating the secretion of insulin, increasing β-cells mass, inhibiting the secretion of glucagon, reducing the rate gastric emptying levels and inducing

satiety. However, GLP-1 is rapidly metabolized by enzyme called dipeptidyl peptidase IV (DPP-IV) into inactive forms. Therefore the GLP-1 has a short half-life of about 1-2 min. DPP-IV inhibitors maintain the level of endogenous active GLP-1 levels and prolongs its half life (5).

Dipeptidyl Peptidase IV (DPP-IV) inhibitor is a new treatment for type 2 diabetes mellitus. Inhibition of DPP-IV can increase levels of active GLP-1. GLP-1 can increase insulin secretion and reduce glucagon secretion, by reducing glucose levels in blood. Synthetic DPP-IV inhibitors show several side effects. Herbal medicines are alternative medicines over synthetic drugs which can relieve patients. Based on research have been carried all over the world related to the efficacy of herbs treatment of type 2 diabetes mellitus. Oral treatment of type 2 diabetes mellitus from herbal medicines is preferred to be prescribed because plant products have a lower toxicity than conventional medicines, low side effects and low cost (6).

Boesenbergia pandurata Roxb is an Indonesian traditional medicinal plant that can be used to treat various diseases, one of which is antioxidants. This study aims to examine the antidiabetic of Boesenbergia pandurata Roxb which has not been tested especially in DPP-IV inhibitor activity (7). In this research we are in silico methods like molecular docking used to discover the ability of the natural from *Boesenbergia Pandurata Roxb* as treatment diabetes mellitus type 2.

2. Materials and Method

2.1. Protein and Ligan Structure

The 3-D crystal structure of the protein DPP-IV inhibitor (PDB: ID 3WQH) was retrieved from protein data bank (PDB) with situs www.rcsb.org/pdb. The 3-D structure ligan Sitagliptin, Vildagliptin, Saxagliptin, Anagliptin, Alogliptin and molecule in *Boesenbergia pandurata* Roxb Alpinetin, Pinostrobin, Cardamonin, Pinocembrin, Panduratin were download from PubChem Compound Section of National Center for Biotechnology Information (NCBI) with situs https://pubchem.ncbi.nlm.nih.gov/.

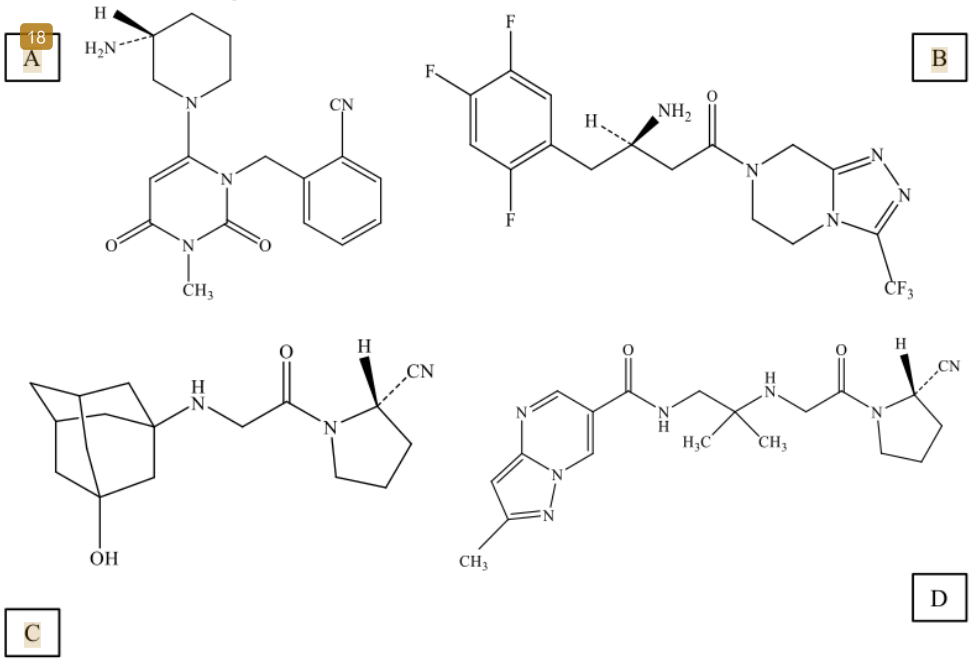
2.2. Molecular Docking

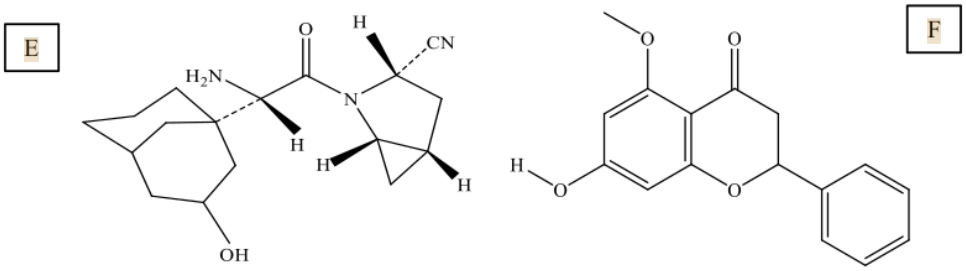
The docking protocol used in this study consisted of the following steps:

1. Preparation of the ligands (construction of 3-D structures, setting the protonation state according with atomic charges employing semi-empirical method namely AM1 with hyperchem software). The ligand used consists of Sitagliptin, Vildagliptin, Saxagliptin, Anagliptin, Alogliptin and active compound *Boesenbergia pandurata* Roxb.
2. Preparation of the macromolecule (The 3-D structure of the DPP-IV protein interaction with Anagliptin was downloaded from the protein data bank which PDB ID is 3WQH (8).
3. The ligand and macromolecule structural is carried out by docking calculations using the Autodock Tools 1.5.6 software (9).
4. Addition of hydrogen atoms based on grid parameters for determine coordinate. What will be calculated are the pairs of energy potential and hydrogen bonds. Protonation of the main residues setting in the active site and running using Autogrid.
5. Analyzing AutoDock results and Reading the Docki log. Procedure klik Analyze next docking next open. Analyze conformations next Load by convention these results files have e extension ".dlg"
6. Analyzing AutoDock results and Visualizing Docked Confor ations. The best docking results can be considered as the lowest energy conformation or can be selected based on RMS deviations from the reference structure. Autodock also breaks the total energy into vander waals energy and electrostatic energy for each atom.
7. Analysis of AutoDock results and clustering conformation. To see the convergence of docking results, it can be seen from clustering. Docking convergence reflects into search. One result of docking is torsion of energy. The greater the torsion needed by the ligand, the greater the number of evaluations needed in the docking process.

3. Results and Discussion

The 2D structure of ligands (Alogliptin, Sitagliptin, Anagliptin, Vildagliptin, Saxagliptin) drug contain DPP-IV inhibitor is available in market and family bioactive compounds of flavonoid such as (Alpinetin, Pinostrobin, Cardamonin, Pinocembrin, Panduratin) found in *Boesenbergia Pandurata* Roxb can be shows in figure 1.





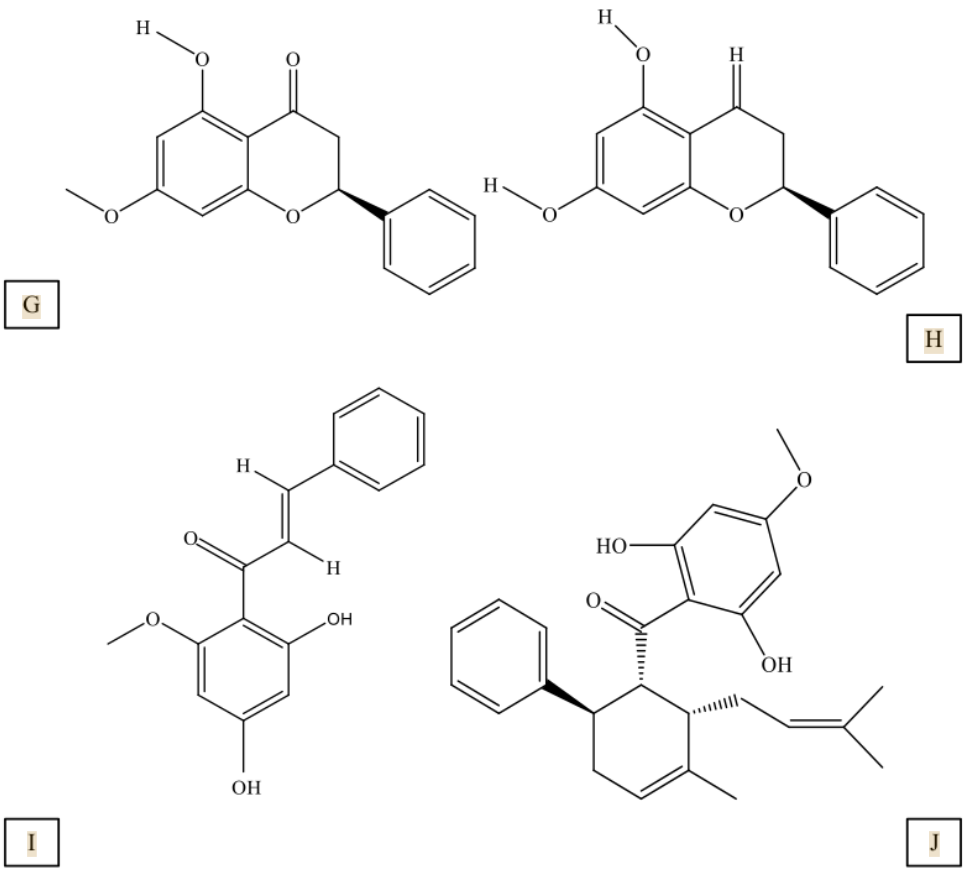


Figure 1. 2-D structure ligand (A) Alogliptin, (B) Sitagliptin, (C) Vildagliptin, (D) Anagliptin, (E) Saxagliptin, (F) Alpinetin, (G) Pinostrobin, (H) Pinocembrin, (I) Cardamonin, (J) Panduratin

DPP-IV structure complex with anagliptin consisted of two independent protein molecules asymmetric bound in one anagliptin molecule. Three interaction substrates anagliptin with DPP-IV can be shows in figure 2 (1) The first site was S_1 substitution which the cyano group had a dipole bond. The distance between the cyano carbon atoms and Oγ with the catalytic residue of Ser630 was 3.8 Å and the distance between the cyano nitrogen atoms and O^{η} with catalytic residues of Tyr547 is 3.2 Å. (2) The second site was S_2 substitution which the secondary amine form double salt bridges with a distance of 3.0 and 3.3 Å between the nitrogen atom of the secondary amine and each Oε of Glu205 and Glu206. (3) The third site was the substitution of S_2 extensive which carbonyl group bound to the pyrazolopyrimidine ring formed a hydrogen bond with N^{η} from Arg358 and the pyrazolopyrimidine ring interaction Π-Π stacking interaction with phenyl ring of Phe357 (8).

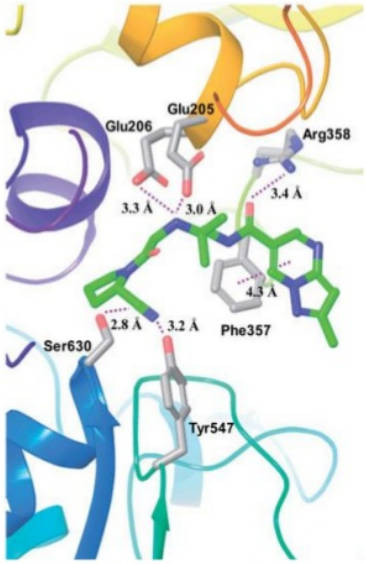


Figure 2. Interaction of anagliptin in the active site of DPP-IV

3.1. Molecular docking

Inhibitor DPP-IV activity was evaluated by *in silico* study. Ligand used such as sitagliptin, vildagliptin, saxagliptin, anagliptin, alogliptin and active compound from *Boesenbergia Pandurata Roxb* such as alpinetin, pinostrobin, cardamonin, pinocembrin, panduratin were docked with DPP-IV as protein and the results can be seen in table 1.

Docking results show that vildagliptin and anagliptin have greater energy binding is 15.49 and 10.11 Kcal/mol among other ligand (saxagliptin, alogliptin, sitagliptin) compounds. Which the active ligand compounds *Boesenbergia Pandurata* Roxb panduratin and cardamonin have a greater binding energy is 2.39 and 1.79 Kcal/mol compared to other ligand compounds. The differences in each parameter value caused the distinction in inhibitory activity in DPP-IV and have a lower value internal energy.

Tabel 1. Molecular docking of ligan with DPP – IV

Active Compounds	Binding Energy (Kcal/mol)	Intermolecular Energy	Internal Energy	Torsional Energy
Vildagliptin	15.49	-4.19	-0.99	19.69
Anagliptin	10.11	-1.22	-0.36	11.34
Alogliptin	1	-0.27	-2.16	2.39
Sitagliptin	1.6	-0.19	-2.94	1.79
Saxagliptin	0.99	-0.21	-2.09	1.19
Panduratin	2.39	0.0	-3.35	5.5
Cardamonin	1.79	0.0	-1.35	5.22
Alpinetin	0.89	0.0	-0.46	5.23
Pinostrobin	0.89	0.0	-1.1	5.07
Pinocembrin	0.89	0.0	-1.01	5.02

Boesenbergia pandurata Roxb is one of *Zingiberaceae* family, herbal plants contain saponin and flavonoid compounds such as pinostrobin, pinocembrin, alpinetin, cardamonin, and panduratin. Five active compound *Boesenbergia pandurata Roxb* which can be obtained from extraction and purification methods. All of them are classified into secondary metabolite groups and can be used to cure diseases (7).

Herbal medicines are alternative medicines besides synthetic drugs that can relieve patients in the treatment of type 2 diabetes mellitus. The use of herbal medicines have minor side effects when given in large doses (6).

4. Conclusion

Based on research conducted from five ligands (Alogliptin, Sitagliptin, Anagliptin, Vildagliptin, Saxagliptin) drugs containing DPP-IV inhibitors are available on the market. The best binding energy is vildagliptin 15.49 and torsional energy 19.69 compared to five ligands active compounds Boesenbergia Pandurata Roxb such as (Alpinetin, Pinostrobin, Cardamonin, Pinocembrin, Panduratin). The best results is Panduratin which has binding energy of 2.39 and torsional energy 5.5 suggested is good prospects for the treatment of type 2 diabetes mellitus. Therefore, further research and studies are needed in vitro and clinics.

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